REMARKS

Claims 1 and 3-24 remain in the Application. Claim 2 has been cancelled. No new subject matter has been added.

CLAIM OBJECTIONS

The Examiner has objected to Claims 4-8 and 19 under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim depends from another multiple dependent claim. Applicants have amended the claims in order to overcome the objection. Reconsideration is respectfully requested.

CLAIM REJECTIONS 35 U.S.C. §§ 101 and 112.2

First Rejection

The Examiner has rejected Claims 20, 21 and 24 under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which Applicants regards as their invention. Applicants have amended Claims 20, 21 and 24 in order to include the process of making the amorphous atorvastatin calcium in the claim and therefore reconsideration of Claims 20, 21 and 24 is respectfully requested.

Similarly, the Examiner has rejected Claims 20, 21 and 24 under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. Applicants have amended Claims 20, 21 and 24 in order to overcome this rejection by inserting the process of forming the amorphous atorvastatin calcium and therefore reconsideration of Claims 20, 21 and 24 is respectfully requested.

Second Rejection

The Examiner has rejected Claim 1 under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which Applicants regarded as their invention. The

term "atorvastatin lactone of formula II" in claim 1 is a relative term which renders the claim indefinite. Although it is Applicants' position that the claim when read, in light of the entire application, atorvastatin lactone of formula II would be understood by a person of ordinary skill to be the chemical structure of formula II as depicted in the application as filed; however, Applicants have included the chemical structure of atorvastatin lactone of formula II in Claims 1, 3 and 23. Therefore, reconsideration of Claim 1 is respectfully requested.

The Examiner has indicated that Claim 2 lacks the antecedent basis for the limitation "residual amounts of solvent other than water". Applicants have cancelled this claim from the application and therefore the rejection is moot.

CLAIM REJECTIONS - 35 U.S.C. §103

The Examiner has rejected Claims 1-24 under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 6,087,511. The Examiner has taken the position that:

> Lin et al disclose a novel process for making amorphous atorvastatin hemi calcium salt, noting that the same is useful as an inhibitor of HMG-CoA and therefore, useful in the treatment of hypercholesterolemia (Col. 1, lines 13-21). The disclosed process comprises a beginning with a mixture comprising atorvastatin lactone and methanol reacted with an aqueous solution of sodium hydroxide to form an open-ring sodium salt. The organic layer is discarded and the aqueous layer is extracted with MTBE. When the organic layer is again discarded, the aqueous solution of the sodium salt is heated and to the solution added calcium acetate hemihydrate dissolved in water. Shortly thereafter, the mixture is seeded with a slurry of crystalline atorvastatin. Some time thereafter, the mixture is heated, then cooled, filtered, and wished with a solution of water and methanol followed by water. The resulting atorvastatin solid is dried under a vacuum to give the crystalline form, and through a process disclosed in Example 2, the crystalline form because amorphous atorvastatin (Col. 5, lines 11-65).
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> The adjustment of particular conventional working conditions such as quantity of seeds of amorphous atorvastatin calcium relative to the weight percent of atorvastatin lactone and the stoichiometry of sodium hydroxide relative to the same, and the timing of the hydrolysis reaction are mere matters of routine optimization and judicious selection well within the purview of one of ordinary skill in the art.

> One of ordinary skill in the art would have been motivated to perform the instant invention based on the disclosures in Lin et al because as noted therein, although amorphous atorvastatin solids were known to exist in advance of the advent of crystalline atorvastatin, "the production of amorphous atorvastatin by the previously disclosed processes was not consistently reproducible (Col. 1, lines 61-65). Further, it was also known that the bioavailability patterns of drugs often differ based on whether their forms are amorphous or crystalline, for example, making it desirable to have a procedure for converting the crystalline form to the amorphous form (Col. 2, lines 1-7).
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> In view of the foregoing, it would have been *prima facie* obvious to one of ordinary skill in the art to prepare amorphous atorvastatin calcium by the hydrolysis of atorvastatin lactone to form atorvastatin sodium salt, to suspend the same into a solution of aqueous calcium acetate, and then, to isolate and dry the same to form amorphous atorvastatin calcium salt and that the same would be effective in the treatment of hypercholesterolemia.

Applicants respectfully submit that the teachings of US Patent No. 6,087,511 actually teach away from the current invention.

The Examiner is directed to column 5, lines 10-64 which provides the process outlined in US 6,087,511 (the '511 Patent). Essentially, the '511 Patent first reacts a mixture of atorvastatin lactone, methyl tertiary-butyl ether and methanol with an aqueous solution of sodium hydroxide to form the ring-opened sodium salt. After separation and extraction, a solution of calcium acetate hemihydrate dissolved in water is added to the methyl tert butyl ether saturated aqueous solution of the sodium salt and heated for at least 30 minutes. The mixture is then seeded with a slurry of crystalline form I atorvastatin, heated again and then cooled, filtered, washed and then the solid is dried and isolated under vacuum for 3-4 days to give crystalline form I atorvastatin.

Example 2 of the '511 Patent dissolves the crystalline form I atorvastatin with agitation and tetrahydrofuran at ambient temperature under a nitrogen atmosphere. Toluene is then added slowly once solution is achieved. The solution is then rinsed to the dryer with additional tetrahydrofuran, full vacuum is applied and the solution

is concentrated at 35°C with mild agitation. The product turns into a brittle glassy foam. The agitator is then used to break the brittle foam into a free flowing powder, the powder is then agitated and the temperature is raised to 85°C under vacuum to loosen the residual solvent levels. Then, after four days of drying, the free-flowing white powder is unloaded from the dryer and the product is amorphous. Applicants respectfully submit that this process is a two step process which requires specialized drying equipment to get an amorphous product over an 8 day period. As well, in forming the atorvastatin calcium, the calcium acetate solution is added to the atorvastatin sodium solution. This is totally contrary to Applicants' invention where it is stated, and as found in Claim 1, a process for the preparation of amorphous atorvastatin calcium comprising hydrolysis of atorvastatin lactone of formula II to form atorvastatin sodium salt solution, addition of the atorvastatin salt solution to an aqueous calcium chloride or calcium acetate solution and isolation by filtration and drying to form amorphous atorvastatin calcium salt.

It is clear throughout the reading of the examples of Applicants' invention, the unexpected advantages of the present invention relative to the prior art include but are not limited to elimination of the solvent removal step after atorvastatin lactone hydrolysis which is clearly found in Example 1 of the '511 Patent, faster filtration of the amorphous atorvastatin calcium which is found in Example 2 of the current application, the filtration and washing steps compared to the prior art conventional formation of atorvastatin calcium were reduced by 71% and in Example 3, the filtration and washing steps were reduced by 53%.

Therefore, the step reversal addition (adding the atorvastatin salt solution to the calcium chloride or calcium acetate solution), as well as Applicants' direct one step process versus the two step process found in the '511 Patent is not obvious to a

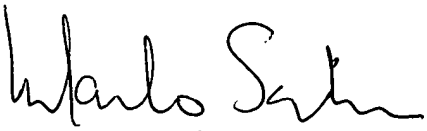
person of ordinary skill in the art. The person of ordinary skill in the art would not have expected that reversal of addition; namely, the addition of the atorvastatin sodium salt solution to an aqueous calcium chloride or calcium acetate solution versus the prior addition of the aqueous calcium solution to the atorvastatin sodium salt solution would have resulted in the direct formation of amorphous atorvastatin, as well as a substantial reduction of processing time when forming the amorphous atorvastatin.

Therefore, in light of the above reconsideration of the claims is respectfully requested.

If the Examiner has any questions, she is respectfully requested to contact Applicants' Agent, Marcelo K. Sarkis at (905) 771-6414 collect at her convenience.

Respectfully submitted,

IVOR M. HUGHES



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Enclosures
Petition for Extension of Time Under 37 CFR 1.136(a)
Check for $1,050.00 US